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EXAMINER	
WORLEY, CATHY KINGDON	

ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,448	FOGHER	
	Examiner	Art Unit	
	Cathy K. Worley	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-75* is/are pending in the application.

4a) Of the above claim(s) *70-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignments*.

DETAILED ACTION

1. The amendment filed May 25, 2007 has been entered.

2. Claims 1-51 have been canceled.

Claims 52-75 have been newly added

New claims 52-69 are drawn to the elected invention.

Claims 52-75 are pending.

Claims 70-75 are withdrawn because they are not directed to the elected invention.

3. Claims 52-69 are examined in the present office action.

4. The text of those sections of Title 35, U.S. Code not included in this office action can be found in a prior office action.

Restriction/Election

5. The Applicant argues the new claims have overcome the lack of inventive step, and therefore, unity of invention is present for all new claims (see second paragraph on page 12 of the response received on May 25, 2007). This is not persuasive, because the instant claims lack an inventive step (see 103 rejection below). The restriction requirement is maintained and is MADE FINAL.

Objections and Rejections that are Withdrawn

6. The objections to the specification for the use of trademarks and for minor informalities are withdrawn in light of the Applicant's amendments to the specification.

7. The objection to the abstract is withdrawn in light of the Applicant's amendment of the abstract.

8. All objections and rejections of the claims are withdrawn because all of the claims examined in the previous Office Action have been cancelled.

Claim Objections

9. Claims 52, 61, and 68 are objected to because of informalities. In light of the specification, the Examiner is able to interpret the claims for the purposes of examination, however, the wording is awkward and technically or grammatically incorrect in places. If the Applicant makes the changes that are requested, below, these objections will be withdrawn.

- In claim 52, please delete "the use of" from line 2, and please replace "a DNA sequence encoding a signal sequence of SEQ ID No. 7" with - - the nucleic acid

of SEQ ID NO:7 - - . This amendment is necessary because a signal sequence is an amino acid sequence, however, SEQ ID NO:7 is a nucleic acid sequence, therefore "a signal sequence of SEQ ID NO:7" is technically incorrect.

- In claim 61, please insert - - the - - between "seed of" and "genetically modified" in line 1; and please insert - - wherein - - before "said enzyme" in line 10. These words appear to have been omitted accidentally, and they are required for the claim to be grammatically correct.
- In claim 68, please replace "dispatch" with - - target - - in line 6, and please delete the dash (-) between "and" and "using" in line 11. This amendment is necessary to utilize art-accepted terminology.

Claim Rejections - 35 USC § 112

10. Claims 59, 63, and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 59 and 68 recite the limitation "said lysosomal enzyme deleted of the native signal sequence" in part "c.". There is insufficient antecedent basis for this limitation in the claim.

Claim 63 recites the limitation "the structural portion of the mature lysosomal enzyme" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

11. Claims 52-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. All dependent claims are included in these rejections.

The claims are broadly drawn to a transformed plant that comprises an expression vector comprising "a" promoter of SEQ ID NO:6, "a" DNA sequence encoding "a" signal sequence of SEQ ID NO:7, and a DNA sequence encoding a lysosomal enzyme lacking its native signal sequence, and to methods and seeds comprising said expression vector.

The Applicant is advised that the use of the article "a" in front of a nucleic acid or amino acid sequence renders it inclusive of fragments as small as dinucleotides or dipeptides. This written description rejection will be withdrawn if the claims are amended to recite "the promoter of SEQ ID NO:6" and "the nucleic acid of SEQ ID NO:7". Please note the claim objection, above, because the current recitation implies that SEQ ID NO:7 is an amino acid sequence which is not correct.

The Applicants describe a plant expression cassette comprising a promoter of the basic 7S soy globulin gene which they refer to as PGLOB and describe as SEQ ID NO:6 (see page 18, lines 2-3), and they describe a nucleic acid encoding a signal sequence from the basic 7S soy globulin (SEQ ID NO:7) (see page 18, lines 3-5). They describe plasmids comprising an expression cassette comprising this promoter operably linked to a polynucleotide encoding this signal sequence fused to glucocerebrosidase (see pages 20-21 and figures 1-3). They describe transgenic tobacco plants transformed with this expression cassette (see pages 22-23). They also describe a plasmid comprising an expression cassette comprising this promoter operably linked to a polynucleotide encoding this signal sequence fused to α-galactosidase A (see pages 27-28 and figure 4); and transgenic tobacco plants transformed with this plasmid (see page 28, lines 11-17). They also describe a plasmid comprising an expression cassette comprising this promoter operably linked to a polynucleotide encoding this signal sequence fused to α-glucosidase A (see pages 28-19 and figure 5).

The Applicants do not describe any promoters other than SEQ ID NO:6; they do not describe any nucleic acids encoding signal sequences other than SEQ ID NO:7. They do not describe any fragments of SEQ ID NO:6 or SEQ ID NO:7 that retain promoter or signal sequence function.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated

that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F. 3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

However, the instant specification describes only one promoter, that of SEQ ID NO:6. The instant specification describes only one signal sequence, that encoded by SEQ ID NO:7.

The Applicants fail to describe a representative number fragments of SEQ ID NOs: 6 and 7 which are encompassed by the current recitation. The Applicants only describe the promoter of SEQ ID NO:6 and the signal sequence encoded by SEQ ID NO:7. Furthermore, the Applicants fail to describe structural features common to members of the claimed genus of promoters and claimed genus of signal sequences. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for promoter activity in seeds or for correct protein targeting and post-translational modifications, it remains unclear what features identify promoters and signal sequences capable of such activity. Since the genus of promoters and genus of signal sequences have not been described by specific structural features,

the specification fails to provide an adequate written description to support the breadth of the claims.

12. Claims 52-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plant transformed with the promoter of SEQ ID NO:6 operably linked to the polynucleotide of SEQ ID NO:7 which is fused in-frame to a polynucleotide encoding a lysosomal enzyme, does not reasonably provide enablement for a transformed plant that comprises an expression vector comprising any promoter or SEQ ID NO:6, any signal sequence of SEQ ID NO:7, and a sequence encoding a lysosomal enzyme which does not necessarily have to be fused in-frame to the signal sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the

relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are broadly drawn to a transformed plant that comprises an expression vector comprising "a" promoter of SEQ ID NO:6, "a" DNA sequence encoding "a" signal sequence of SEQ ID NO:7, and a DNA sequence encoding a lysosomal enzyme lacking its native signal sequence, and to methods and seeds comprising said expression vector.

The Applicant is advised that the use of the article "a" in front of a nucleic acid or amino acid sequence renders it inclusive of fragments as small as dinucleotides or dipeptides. Also, the recitation in claims 54 and 63 of "wherein the DNA sequence encoding the signal sequence is fused in-frame to the sequence encoding the structural portion of the mature lysosomal enzyme" demonstrates that independent claim 52 and claim 61 include vectors wherein the sequences are not fused in-frame. This enablement rejection will be withdrawn if the claims are amended to recite "the promoter of SEQ ID NO:6" and "the nucleic acid of SEQ ID NO:7 and a recitation that the DNA sequence encoding the lysosomal enzyme is fused in-frame with SEQ ID NO:7. Please note that claims 54 and 63 will become substantial duplicates if this suggested amendment is made to claims 52 and 61.

Applicants teach a plant expression cassette comprising a promoter of the basic 7S soy globulin gene which they refer to as PGLOB and describe as SEQ ID NO:6 (see page 18, lines 2-3), and they teach a nucleic acid encoding a signal

sequence from the basic 7S soy globulin (SEQ ID NO:7) (see page 18, lines 3-5). They teach plasmids comprising an expression cassette comprising this promoter operably linked to a polynucleotide encoding this signal sequence fused to glucocerebrosidase (see pages 20-21 and figures 1-3). They teach transgenic tobacco plants transformed with this expression cassette (see pages 22-23). They also teach a plasmid comprising an expression cassette comprising this promoter operably linked to a polynucleotide encoding this signal sequence fused to α-galactosidase A (see pages 27-28 and figure 4); and transgenic tobacco plants transformed with this plasmid (see page 28, lines 11-17). They also teach a plasmid comprising an expression cassette comprising this promoter operably linked to a polynucleotide encoding this signal sequence fused to α-glucosidase A (see pages 28-19 and figure 5).

Applicants do not teach any promoters other than SEQ ID NO:6; they do not teach any nucleic acids encoding signal sequences other than SEQ ID NO:7. They do not teach any fragments of SEQ ID NO:6 or SEQ ID NO:7 that retain promoter or signal sequence activity.

The prior art teaches that the 7S globulin from soybean is also referred to as β-conglycinin (see Hayashi et al. (1998) MGG, Vol. 258, pp. 208-214, abstract). The prior art teaches that this protein is comprised of three subunits;α', α, and β (see Chen et al. (1989) Developmental Genetics, Vol. 10, pp. 112-122, abstract). Chen et

al. teach that both the α'and β subunits accumulated during mid-to-late stages of seed development (see abstract).

Given the lack of guidance in the instant specification, undue trial and error experimentation would be required for one of skill in the art to determine which polynucleotide fragments of SEQ ID NO:6 would have promoter activity. It would require undue experimentation to screen through every fragment, as small as dinucleotides, to determine which pieces comprise promoter activity. Undue trial and error experimentation would also be required to determine what fragments of SEQ ID NO:7 encode signal sequences that provide the function of "dispatching" or targeting a lysosomal enzyme to seed storage organs and providing unspecified post-translational modifications required for the expression of the lysosomal enzyme in active form.

With regard to the promoters encompassed by the instant claims, deletion analysis of various promoters have shown that even DNA segments from the portion of a promoter region containing sequence elements thought to be most important (*e.g.*, the TATA-box) need to have sufficient length and comprise additional sequences. Maiti et al (1997, Transgen. Res., 6:143-156), in studies on a figwort mosaic virus promoter, found that the smallest portion upstream of the transcriptional start site of that would support transcription was 198 basepairs long; segments of 73 and 37 basepairs did not work (Fig. 4). Doelling et al (1995, Plant J. 8:683-692) found that the minimal rRNA promoter of *Arabidopsis thaliana*

is at least 33 nucleotides long (Fig. 1). Therefore the prior art teaches that there is a high degree of unpredictability with regard to the minimal length of the sequences upstream of a coding region that is required for promoter activity. The Examiner is not aware of any published results demonstrating promoter activity for nucleic acids as small as dinucleotides.

With regard to claims 52 and 61, in particular, these claims encompass vectors in which the nucleic acid encoding the signal sequence is not necessarily fused in-frame with the nucleic acid encoding the lysosomal enzyme. One of skill in the art would not know how to use such a vector, because the signal sequence cannot function unless it is expressed as a fusion protein with the coding sequence, and in order for this to happen, the nucleic acids must be fused in-frame.

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to make the claimed invention, and therefore, the invention is not enabled throughout the broad scope of the claims.

Claim Rejections - 35 USC § 103

13. Claims 52-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radin et al. (US Patent No. 5,929,304, issued on Jul. 27, 1999) in view of Watanabe (GenBank Accession D16107, published on Feb. 1, 2000), further in view of Fogher

(WO 00/04146, published on Jan. 27, 2000), and further in view of Whitelam GC (J. Sci. Food Agric. (1995) Vol. 68, pp. 1-9).

The claims are drawn to a transformed plant that comprises an expression vector comprising a promoter of SEQ ID NO:6 (which is a promoter from the soybean basic 7S globulin gene), a signal sequence of SEQ ID NO:7 which is able to dispatch an enzyme to seed storage organs and to provide the post-translational modifications required for enzymatic activity, and a sequence encoding a lysosomal enzyme.

Radin et al. teach plants transformed with a recombinant expression construct encoding a lysosomal enzyme (see claim 33). They teach the production of enzymatically active recombinant lysosomal enzymes of both human and animal origin (see abstract). They teach the use of several different signal peptides (see column 14, lines 31-67 and column 15, lines 1-9). They teach the removal of the signal peptide (see column 14, lines 33). They teach expression vectors that are plasmids (see column 22, line 1). Rabin et al. teach plants expressing any one of a list of lysosomal enzymes (see claims 26, 27, 47, and 48), and this list includes glucocerebrosidase, which is recited in the instant claims and reduced to practice in the instant application. They specifically teach transgenic tobacco plants expressing a lysosomal enzyme (see columns 21-25). They teach a seed of such a plant (see claims 54-57).

Radin et al. do not teach a promoter of SEQ ID NO:6, nor do they teach expression in an amount of at least 0.8% of seed extracted total proteins, nor do they teach a signal sequence of SEQ ID NO:7.

Watanabe teaches the soybean basic 7S globulin promoter that comprises SEQ ID NO:6 (see sequence alignment).

Fogher teaches the signal sequence encoded by SEQ ID NO:7 (see sequence alignment). Fogher teaches that expression cassettes were made with regulation elements from the 7S basic globulin gene (see second paragraph on page 23, and entire document). Fogher teaches that yields of 1% to 1.8% of seed total storage proteins were achieved for a recombinant protein expressed utilizing these regulatory elements (see first paragraph on page 22).

At the time the invention was made, it would have been obvious and within the scope of one of ordinary skill in the art to modify the plants taught by Radin et al. to substitute the soybean basic 7S globulin promoter and signal sequence for the promoters and signal peptides taught by Radin et al.

In the prior art, Radin et al teach plants, seeds, and methods that differ from the instant invention only by the promoter and signal sequences utilized.

At the time the invention was made, the promoter from the soybean 7S globulin gene (SEQ ID NO:6) and the nucleic acid sequence encoding the signal peptide (SEQ ID NO:7) were known in the art (taught by Watanabe and Fogher, respectively). Their functions as a seed-preferred promoter and as a signal

sequence capable of targeting proteins through the secretory pathway to yield properly glycosylated recombinant proteins were known in the art (see Fogher: paragraph bridging pages 19-20, and page 21, and paragraph bridging pages 29-30).

At the time the invention was made, one of ordinary skill could have substituted the promoter sequence taught by Watanabe and the signal sequence taught by Fogher for the regulatory elements utilized by Radin et al. One of ordinary skill would have predicted producing a higher yield of recombinant protein in the seeds of the resulting transgenic plant, based on the teachings of Fogher et al (see first paragraph on page 22).

One of ordinary skill in the art would have had additional motivation for this design choice because Whitelam teaches that expression of valuable recombinant enzymes in seeds is desirable because the recombinant enzymes can be stored for long periods in dry seeds (see page 8, second paragraph). Whitelam discusses "bio-farming" in general (see abstract and page 2, second paragraph), and specifically teaches that there are advantages to seed-localized expression of recombinant proteins (see page 2, right column).

Given the successes and advantages of expressing recombinant enzymes in seeds, taught by Whitelam, one would have expected to succeed in expressing the lysosomal enzymes taught by Radin in seeds. Given the success of Fogher in expressing a recombinant protein utilizing regulatory elements from the soybean

basic 7S globulin gene, one would have had an expectation of success in utilizing SEQ ID NOs: 6 and 7 as regulatory elements.

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cathy K. Worley whose telephone number is

(571) 272-8784. The examiner is on a variable schedule but can normally be reached on M-F 10:00 - 4:00 with additional variable hours before 10:00 and after 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CKW

ANNE MARIE GRUNBERG
SUPERVISORY PATENT EXAMINER